INFLUENCE OF ADSORBED CHARGES AND DIPOLES ON THE GATING CHARGES IN EXCITABLE MEMBRANES

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1. Introduction

It has been suggested [1] and experimentally verified [2–4] that the opening of ionic channels in nerve membranes is associated with the movement of charges, so-called gating charges, within the membranes. In this communication we will use this observation to deduce some interesting consequences of charges or dipoles adsorbed in the hydrocarbon part of a membrane. We show that the electrostatic potential at a gating charge due to adsorbed charges or dipoles can be of the same order as normally-occurring voltage drops across excitable membranes. The size of this electrostatic potential depends on a number of parameters like the distance between the adsorbed charge or dipole and the gating charge, and the dielectric constant of the region where the adsorption takes place. Possible models are suggested for the action of anaesthetics and drugs on membranes, for the influence of odorant molecules on olfactory receptors and for the excitation of membranes in photoreceptors.

2. Theory

Simple expressions for the electrostatic interaction between a charge or a dipole adsorbed in a membrane and a gating charge belonging to an ionic channel will be developed. The geometrical situation is illustrated in fig.1. To be explicit we assume the gating charge to

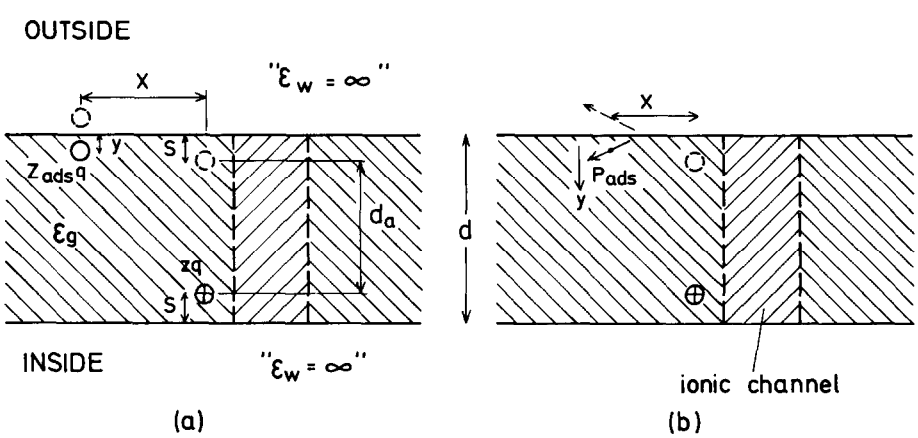

Fig.1. Schematic picture of the adsorption of charges (a) or dipoles (b) in the hydrocarbon part of an excitable membrane. $z_{ads}q$ represents an adsorbed charge. P_{ads} represents an adsorbed dipole. The angle φ in eq. (3) is the angle between the membrane surface and the dipole. zq represents a gating charge on the inside of the membrane. The dashed circle in the membrane illustrates the alternative position of a gating charge. The dashed symbols outside the membrane illustrate the images considered in the derivation of eq. (2) and eq. (3).

be positive. This is no limitation since similar calculations can be made for a negative gating charge as well. The adsorbed charge or dipole is assumed to be in the hydrocarbon part of the membrane but close to the outside (again, similar calculations can be made, for adsorption on the inside). The dipole may be the permanent dipole of an adsorbed molecule or a dipole induced by the adsorption itself. Such induced dipoles, which are well known in surface physics, are partly due to the abrupt change in the dielectric constant on the passage of an interface. The dipole (or charge) may also be induced by an interaction between a specific group in the membrane and an adsorbed molecule.

The (positive) gating charge is assumed to be in one of two positions, either close to the outside or the inside of the membrane as indicated in fig.1. The probability of finding it on the outside, f_{out}, is given by Maxwell-Boltzmann statistics,

$$f_{out} = \frac{1}{1 + e^{-zq\,(\phi + V_a)/kT}} \qquad (1)$$

where V_a is the voltage drop across the 'active' part of the membrane, d_a, due to an externally applied voltage V (V positive when the inside is positive with respect to the outside), ϕ is the potential energy difference of the gating charge between the inside and outside, respectively, without applied voltage. ϕ contains a term ϕ_o, dependent on the properties of the gating system (or ionic channel) itself, incorporating electrostatic interaction between the gating charges [5], and a term ϕ_{ads} due to the adsorbed charge or dipole. If, for simplicity, y is assumed to be small compared to s, and x and $s \ll d$, where y,s,x and d are defined in fig.1 then,

$$\phi_{ads} \approx -\frac{z_{ads}\, q\, y}{2\pi\epsilon_g\, \epsilon_o} \frac{s}{(s^2 + x^2)^{3/2}} \qquad (2)$$

for an adsorbed charge (case (a), fig.1) and

$$\phi_{ads} \approx -\frac{P_{ads} \sin\varphi}{2\pi\epsilon_g\, \epsilon_o} \frac{s}{(s^2 + x^2)^{3/2}} \qquad (3)$$

for an adsorbed dipole (case (b), fig.1).

ϵ_g is the dielectric constant of the membrane (or the area of the membrane between the adsorbed charge and the gating charge). ϵ_o is the dielectric permitivity of free space. z_{ads} and P_{ads} are the valence of the adsorbed charge and the dipole moment of the adsorbed dipole, respectively. $P_{ads} \sin\varphi$ is the component of the dipole moment in the y direction. Equations (2) and (3) were derived with the use of image charges as indicated in fig.1. The electrolyte outside and inside the membrane was regarded as infinitely conducting ($\epsilon_w = \infty$). The assumptions made about y, x and s imply that, for a gating charge close to the outside only, the adsorbed charge or dipole and its closest image have to be considered. Furthermore, with the assumptions made, the influence of the adsorbed charge or dipole on a gating charge at the inside will be very small. Equations (2) and (3) are therefore the electrostatic potential energy of a gating charge on the outside of the membrane due to an adsorbed charge or dipole. The influence of adsorbed charges or dipoles is illustrated in fig.2 where we have

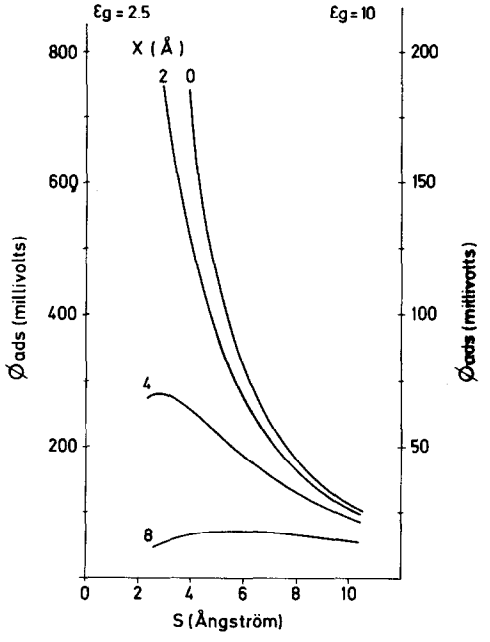

Fig.2. Potential energy difference, ϕ_{ads}, between inside and outside of the membrane for a gating charge due to an adsorbed charge or dipole. ϕ_{ads} is plotted versus the distance of the gating charge from the inside and outside respectively (s, fig.1). The parameter x is the lateral distance between the adsorbed charge or dipole and the gating charge (see fig.1). ϕ_{ads} shown is for $z_{ads} = 1$ and y 1 Å or a dipole with a component in the y direction of −4.85 debye. Two different dielectric constants of the gating region are considered ϵ_g 2.5 (left axis) and ϵ_g 10 (right axis). (Note that $s/(s^2 + x^2)^{3/2}$ has a maximum equal to $2/(3\sqrt{3}\,x^2)$ at $s = x/\sqrt{2}$.)

plotted ϕ_{ads} versus the distance s with x as a parameter. We have chosen $z_{ads} - 1$ and y 1 Å for case (a), fig.1. The drawing also illustrates the influence of a dipole whose component in the y direction is −4.85 debye. The first observation is that ϕ_{ads}, as large as normally-occurring voltage drops across the membrane, is also obtained for adsorption far from the gating charge and even for an 'effective' dielectric constant as high as ϵ_g 10. The adsorption of charges or dipoles influences the distribution of gating charges according to eq. (1). This means in turn that the adsorption may open (or close) ionic channels. The drawings in fig.1 are only schematic. The arguments presented above apply also to so called aggregation models of ionic channels [5–7] where charged monomers or channel-forming segments aggregate to form the channels. Equation (1) represents now the fraction of subunits which are available for aggregation.

3. Discussion

The opening and closing of ionic channels in excitable membranes are almost inevitably connected with the movement of charges within the membrane. We have shown that charges or dipoles adsorbed onto the membrane influence the distribution of these gating charges in the membrane. In our model it is important that the adsorbed charges or dipoles as well as the gating charges reside in a region with low dielectric constant.

Dipoles or charges in the electrolyte are effectively screened by the dielectric constant of water and the conductivity of the electrolyte. On the other hand adsorption close to the water/hydrocarbon interface gives rise to large electrostatic interaction energies as seen from eq. (2), eq. (3) and fig.2.

The influence of an adsorbed charge or dipole on a gating charge depends on the sign, size and position of the charge or dipole with respect to the gating charge. It is seen in fig.2 that adsorption directly above a gating charge gives a particularly large influence as expected.

Figure 2 was drawn for an adsorbed charge (z_{ads} −1) at a distance of 1 Å from the water/hydrocarbon interface or a dipole with a dipole moment of −4.85 debye perpendicular to the membrane. Equations (2) and (3) indicate, however, how different adsorption parameters change the interaction. It is furthermore possible that more than one adsorbed charge or dipole influence the same gating charge. It is obvious, however, that interaction energies of magnitude larger than normally-occurring voltages across membranes are readily obtained. The adsorbed charges or dipoles will therefore influence the distribution of gating charges across the membrane and hence the number of open channels at a given 'externally' applied voltage. The adsorption of charges or dipoles may be on special adsorption sites connected with the gating system or ionic channel.

The considerations in this communication suggest simple models for the action of 'drugs' on excitable membranes. A special case is the adsorption of molecules on or in the membrane of the olfactory receptor cells. It is realized that the proposed interaction between adsorbed charges or dipoles and charges within a membrane will be very versatile in explaining the vastly different smell of only slightly different molecules. A change in orientation of an adsorbed dipole will, for example, change the interaction energy and therefore the number of open channels or the fraction of time a single channel is open. Furthermore the idea of induced dipoles can explain the 'smell' of symmetric molecules with no permanent dipole moment or charge.

Another possibility is that the adsorption of charges in the hydrocarbon region is involved in the normal opening and closing of ionic channels in nerve membranes. In this case we have to assume a voltage-dependent adsorption of ions normally present in the electrolyte on special sites in the membrane close to the gating charges. On a change in voltage across the membrane the number of adsorbed ions change, thereby changing the number of open channels.

A further implication of the calculations is connected with 'bleaching' of rhodopsin. On the adsorption of a photon the rhodopsin molecule undergoes a conformational change, which is associated with a charge displacement in the molecule [8]. These charge displacements give rise to a small photopotential, the 'early receptor potential' [9,10]. This potential is, however, rather small and cannot be the direct cause of the opening or closing of normal ionic channels. If, on the other hand, the charge displacement in the rhodopsin molecules affects gating charges in the way suggested in this communication then a

mechanism is found which can explain the excitation of the receptor. As a matter of fact there are numerous experiments and theoretical models which suggest photon-induced opening (or closing) of ionic channels as a possible mechanism for the excitation of photoreceptors (for a review, see [11]).

In conclusion, we should like to stress that the treatment of the events in excitable membranes as 'local' phenomena and not only in terms of potential differences across the membranes may, give new insight in many processes of biological significance.

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